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The Journal of Urology (ISSN 0022-5347) is the Official Journal of the American Urological Association, Inc., and is published monthly by Williams & Wilkins, 428 East Preston Street, Baltimore, MD 21202. Second class postage paid at Baltimore, MD, and at additional mailing offices. Subscription rates individual \$193.00 (\$258.00 foreign); institutions \$215.00 (\$280.00 foreign); in-training \$95.00 (\$160.00 foreign); single copy \$23.00 (\$28.00 foreign). Foreign prices exclude Japan (See Information for Subscribers). Printed in USA. Subscription prices subject to change. The GST number for Canadian subscribers is 123394371. To order call 1-800-638-6423 from anywhere in the U.S.; in Maryland call 1-800-638-4007. POSTMASTER: Send address changes to The Journal of Urology, 428 East Preston Street, Baltimore, MD 21202. Indexed by *Current Contents*, *Index Medicus*, *Excerpta Medica* and *Biosis*. Printed on acid-free paper. Copyright © 1993 by American Urological Association, Inc.

The Journal of UROLOGY

Volume 149

May 1993

Number 5, Part 2 of 2

Foreword. *S. S. Howards* 1237

IMPOTENCE

State of the Art Article

Venous Impotence: Pathophysiology, Diagnosis and Treatment. *E. Wespes and C. Schulman* 1238

Review Article

Review of Erectile Dysfunction: New Insights and More Questions. *S. E. Lerner, A. Melman and G. J. Christ* 1246

Editorial. Erectile Dysfunction: Problems and Challenges. *T. F. Lue* 1256

Evaluation

Diagnosis and Treatment of Psychogenic Erectile Dysfunction in Urological Setting: Outcomes of 18 Consecutive Patients. *M. A. Vickers, Jr., A. M. De Nobrega and R. G. Dluhy* 1258

Evaluation of Penile Deep Arteries in Psychogenic Impotence by Means of Duplex Ultrasonography. *F. Iacono, S. Barra and T. Lotti* 1262

Comparison of RigiScan and Formal Nocturnal Penile Tumescence Testing in Evaluation of Erectile Rigidity. *R. P. Allen, J. K. Smolev, R. M. Engel and C. B. Brendler* 1265

Predictive Value of Real-Time RigiScan Monitoring for Etiology of Organogenic Impotence. *M. Djamilian, C. G. Stief, U. Hartmann and U. Jonas* 1269

Posttraumatic Impotence: Magnetic Resonance Imaging and Duplex Ultrasound in Diagnosis and Management. *N. A. Armenakas, J. W. McAninch, T. F. Lue, C. M. Dixon and H. Hricak* 1272

Evaluation of Vasculogenic Impotence by Monitoring of Cavernous Oxygen Tension. *H. H. Knispel and R. Andresen* 1276

Prostaglandin E1 and Nitric Oxide Donor Linsidomine for Erectile Failure: Diagnostic Comparative Study of 40 Patients. *H. Porst* 1280

Editorial. Impotence Evaluation. *W. D. Steers* 1284

Therapy

Negative Pressure Device for Erectile Disorders: When Does it Fail? *W. Meinhardt, A. A. B. Lycklama a Nijeholt, R. F. Kropman and J. Zwartendijk* 1285

Intracavernous Pharmacotherapy for Impotence: Selection of Appropriate Agent and Dose. *B. von Heyden, C. F. Donatucci, N. Kaula and T. F. Lue* 1288

Four-Drug Intracavernous Therapy for Impotence due to Corporeal Veno-Occlusive Dysfunction. *F. Montorsi, G. Guazzoni, F. Bergamaschi, L. Ferini-Strambi, L. Barbieri and P. Rigatti* 1291

Followup Results of Combination of Calcitonin Gene-Related Peptide and Prostaglandin E1 in Treatment of Erectile Dysfunction. *M. Djamilian, C. G. Stief, M. Kuczyk and U. Jonas* 1296

Sodium Bicarbonate Alleviates Penile Pain Induced by Intracavernous Injections for Erectile Dysfunction. *E. Z. Moriel and J. Rajfer* 1299

Long-Term Results of Penile Vein Ligation for Impotence From Venous Leakage. *A. L. Freedman, F. C. Neto, C. M. Mehringer and J. Rajfer* 1301

Hydroflex Penile Prosthesis: Test Case for Introduction of New Urological Technology. *M. Riehmman, T. C. Gasser and R. C. Bruskewitz* 1304

Analysis of Microsurgical Penile Revascularization Results by Etiology of Impotence. *M. S. Cookson, D. L. Phillips, M. E. Huff and W. P. Fitch, III* 1308

Editorial. Impotence Therapy. *D. K. Montague* 1313

Complications

Development of Peyronie's Disease With Use of Vacuum Constriction Device. *J. H. Kim and C. C. Carson, III* 1314

Pulmonary Migration of Coils Inserted for Treatment of Erectile Dysfunction Caused by Venous Leakage. *E. Z. Moriel, C. M. Mehringer, M. Schwartz and J. Rajfer* (Editorial Comment by D. K. Montague) 1316

Peyronie's Disease

Results of Combined Nesbit Penile Plication With Plaque Incision and Placement of Dacron Patch in Patients With Severe Peyronie's Disease. *G. J. Faerber and J. W. Konnak* 1319

Peyronie's Plaque: Surgical Treatment With Carbon Dioxide Laser and Deep Dorsal Vein Patch Graft. *G. R. Fournier, Jr., T. F. Lue and E. A. Tanagho* 1321

Editorial. Peyronie's Disease. *G. S. Benson* 1326

Contents continued on page A6

INFERTILITY

Review Article

Effects of Cancer and Cancer Therapy on Male Reproductive Function. <i>R. A. Costabile</i>	1327
--	------

Diagnosis

Antigens in Capacitated Spermatozoa Eliciting Autoimmune Responses. <i>E. W. Wingate, R. T. Patrick and S. Mathur</i>	1331
Correlation Between Round Cells and White Blood Cells in Semen. <i>M. Sigman and L. Lopes</i>	1338
Transrectal Ultrasound in Evaluation of Men With Low Volume Azoospermia. <i>J. H. Worischek and R. O. Parra</i>	1341
Value of Quantitative Testicular Biopsy and Deoxyribonucleic Acid Flow Cytometry in Predicting Sperm Recovery From Electrostimulated Ejaculates. <i>I. H. Hirsch, D. Kulp-Hugues, P. McCue, M. Flanigan, J. Sedor, A. Stevenson and W. E. Staas</i>	1345
Evaluation and Treatment of Infertility in Spinal Cord Injured Men Through Rectal Probe Electroejaculation. <i>J. P. Buch and B. H. Zorn</i>	1350
Editorial. Infertility Diagnosis. <i>L. I. Lipshultz</i>	1355

Therapy

Should Testicular Artery be Preserved at Varicocelectomy? <i>T. Matsuda, Y. Horii and O. Yoshida</i>	1357
Varicocele Vein Ligation in 565 Patients Under Local Anesthesia: Long-Term Review of Technique, Results and Complications in Light of Proposed Management by Laparoscopy. <i>L. S. Ross and N. Ruppman</i> ..	1361
Microsurgical Epididymovasostomy: Predictors of Success. <i>C. Niederberger and L. S. Ross</i>	1364
Microsurgical Aspiration of Sperm From Epididymis: Mobile Program. <i>J. L. Marmar, S. L. Corson, F. R. Batzer, B. Gocial and K. Go</i>	1368
Editorial. Surgical Therapy of Male Infertility. <i>M. Goldstein</i>	1374

The original artwork of Mr. Paul H. Stempen, University of California, San Francisco, that appears on the cover of this special issue is gratefully acknowledged.

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FOLLOWUP RESULTS OF A COMBINATION OF CALCITONIN GENE-RELATED PEPTIDE AND PROSTAGLANDIN E1 IN THE TREATMENT OF ERECTILE DYSFUNCTION

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ABSTRACT

Recent human and animal studies have shown a possible role for calcitonin gene-related peptide in penile erection and a therapeutic benefit in combination with prostaglandin E1 for autoinjection therapy. The ethical committee approved calcitonin gene-related peptide-prostaglandin E1 combination for cases of nonresponse or cavernous fibrosis to papaverine-phentolamine. Since June 1990, 65 patients (59 nonresponders and 6 with fibrosis) were injected with 5 μ g. calcitonin gene-related peptide plus 10 μ g. prostaglandin E1. Of the 59 nonresponders to papaverine-phentolamine 31 and of the 6 patients with fibrosis 5 had full erectile response. Of these 36 patients 2 experienced pain during the pharmacologically induced erection. A total of 39 patients who had had at least 20 autoinjections of calcitonin gene-related peptide plus prostaglandin E1 was available for minimum followup. There were no side effects, such as pain (the 2 patients with pain mentioned previously were not included in the autoinjection therapy group), systemic side effects or (increased) fibrosis. Our results show that a combination of calcitonin gene-related peptide and prostaglandin E1 may be beneficial to the treatment of impotence in carefully selected patients.

KEY WORDS: impotence, penile erection, prostaglandins E, calcitonin gene-related peptide

Since the identification of the neurotransmitters for penile erection would have significant impact on the treatment of erectile dysfunction, research has focused on this topic of pharmaco-mechanical coupling during the last several years.¹⁻⁷ Recently, endothelial derived relaxing factor has been shown to participate in cavernous smooth muscle relaxation.⁸⁻¹² The classical drugs (papaverine, papaverine plus phentolamine and prostaglandin E1) for autoinjection therapy induce a full erectile response in about 50 to 70% of an unselected population of men with erectile dysfunction.¹³⁻²¹ The remaining patients with erectile dysfunction cannot be treated by autoinjection, although they would fit into its selection criteria and be willing to accept this therapeutic option. Therefore, a new drug for intracavernous injection with a higher response rate is needed, at least for the latter patients. Previous studies have shown the combination of prostaglandin E1 with calcitonin gene-related peptide for intracavernous injection to be more effective in inducing an erectile response than papaverine plus phentolamine or prostaglandin E1 alone.²² Therefore, we offered patients not responding to papaverine plus phentolamine with a sufficient erectile response or those with cavernous fibrosis during such therapy a combination of 5 μ g. calcitonin gene-related peptide plus 10 μ g. prostaglandin E1. Our followup data are reported.

PATIENTS AND METHODS

At our impotence clinic all patients undergo a comprehensive noninvasive or semi-invasive diagnostic evaluation. Since we routinely use intracavernous injections of vasoactive drugs for this evaluation, patients with stages III and IV arterial occlusive disease, cardiac dysrhythmias, recent myocardial infarction, sexual deviation, severe psychogenic disorders, addiction, severe liver insufficiency and age older than 65 years were excluded. Case history including a questionnaire and sexual case history by a psychiatrist were taken. Blood laboratory tests, pharmacological tests,²³ single potential analysis of cavernous electric activity²⁴ and Doppler study^{25,26} were performed. Phar-

maco-cavernosometry or angiography was done as needed in select patients.

Pharmacological testing was done in a relaxed atmosphere after the patient was informed about the method and its possible side effects, and written informed consent was obtained. With the patient in the supine position, the first injection was given, which consisted of a low dose of 0.2 ml. of a papaverine (15 mg./ml.)-phentolamine (0.5 mg./ml.) mixture (corresponding to 3 mg. papaverine plus 0.1 mg. phentolamine). Only 1 injection a day was administered to prevent priapism by additive effects, and the patient was advised to restrain from psychogenic or reflexogenic stimulation to allow comparison of the results. If erectile response was insufficient, the dose was augmented to 0.5, 1 and 2 ml., respectively, for the following injections. If 2 ml. (corresponding to 30 mg. papaverine plus 1 mg. phentolamine) did not induce a full erection, the dose was repeated but stimulation was added. The erectile response was evaluated by a urologist based on inspection and palpation, and graded as follows: E0—no response, E1—slight tumescence, E2—medium tumescence, E3—full tumescence, E4—full tumescence with medium rigidity and E5—full erection.

When the high dose of papaverine-phentolamine plus stimulation did not induce an erectile response sufficient for intercourse, the patients were informed about the high likelihood of venous leakage as the etiology of the erectile dysfunction, and the therapeutic options of venous surgery, penile prosthesis and a trial of calcitonin gene-related peptide plus prostaglandin E1 were presented. Marked cavernous fibrosis due to autoinjection therapy with other drugs was the other indication for which the calcitonin gene-related peptide-prostaglandin E1 combination was approved by the Ethical Committee of the Medizinische Hochschule Hannover (approval No. 32). The patients were extensively informed about the experimental nature of this drug combination and possible side effects, such as severe circulatory symptoms or significant cavernous fibrosis. They were told that the intracavernous injection of 1 compound (prostaglandin E1) alone may be tried but the outcome would probably be less effective.²²

If the patient wanted to try the combination, written consent was obtained and he was injected with 5 μ g. calcitonin gene-

Accepted for publication December 11, 1992.
Supported by a grant from the Deutsche Forschungsgemeinschaft DFG St1 96/2-2.

related peptide plus 10 μ g. prostaglandin E1 intracavernously in the supine position without any stimulation. When this dose did not induce a full erectile response, the same amount was injected with additional stimulation after a delay of at least 24 hours. If the calcitonin gene-related peptide-prostaglandin E1 mixture induced an erection sufficient for intercourse, the patients were trained in the handling of the procedure itself and advised to present immediately if a side effect occurred. Due to the experimental nature of the study, followup was done after every 10 autoinjections, and it included specific case history, physical examination, blood pressure measurement and blood laboratory tests. When cavernous fibrosis was suspected by case history or physical examination, high resolution sonography was performed to examine the cavernous bodies.

RESULTS

From September 1988 to May 1992, 59 patients with an insufficient erectile response to 30 mg. papaverine plus 1 mg. phentolamine and stimulation, and 6 with cavernous fibrosis due to autoinjection therapy with papaverine-phenolamine selected the calcitonin gene-related peptide plus prostaglandin E1 combination to restore erectile potency. Of the 59 nonresponders to papaverine-phenolamine 33 achieved a full erection (E5), 21 an almost full erection (E4) and 5 tumescence (E2 or E3) with calcitonin gene-related peptide-prostaglandin E1. Two patients with a full erectile response experienced intrapenile pain but there were no other acute objective or subjective side effects. Of the 6 patients with cavernous fibrosis calcitonin gene-related peptide-prostaglandin E1 induced a full erection (E5) in 5 and medium erection (E3) in 1. No acute side effects were observed in this group.

Due to the inconvenience of the intracavernous injection itself, the insufficient erectile response or the unknown long-term effects of this study only 34 of the 59 nonresponders and 5 of the 6 patients with fibrosis entered the autoinjection program with calcitonin gene-related peptide plus prostaglandin E1. Of 26 patients who completed at least 20 autoinjections 17 had done more than 40 and 9 had done more than 80 injections. No cavernous fibrosis or penile deviation was found subjectively or objectively (palpation) in any of the nonresponders, nor was there any increase in size of the fibrous area (5 patients) or of the penile deviation (2 patients) in the fibrosis group. There were no significant changes in blood laboratory tests and no prolonged erections (duration more than 6 hours).

DISCUSSION

Previous studies have shown the combination of calcitonin gene-related peptide and prostaglandin E1 to be more effective in inducing a full erectile response than the combination of papaverine-phenolamine or prostaglandin E1 alone.²² In our series the combination of 5 μ g. calcitonin gene-related peptide and 10 μ g. prostaglandin E1 induced a full erectile response in 31 of 59 patients (53%) who had had an insufficient response to papaverine-phenolamine. Although we know that prostaglandin E1 is somewhat more effective in inducing a full erectile response, we did not routinely inject intracavernously prostaglandin E1 alone, since the combination of calcitonin gene-related peptide plus prostaglandin E1 appeared to be significantly more effective. This practice is also supported by the 53% rate of full erections with calcitonin gene-related peptide plus prostaglandin E1 in patients who did not respond to papaverine plus phentolamine. This assumption is in accordance with the findings of another group working with the combination of calcitonin gene-related peptide plus prostaglandin E1 but it was used only in patients not responding to 80 mg. papaverine plus 2 mg. phentolamine or to 40 μ g. prostaglandin E1, with a reported success rate of 25%.²⁷ The superior effectiveness of the combination of calcitonin gene-related peptide plus prostaglandin E1 compared to prostaglandin E1 alone, although the amount of prostaglandin E1 in the combination

is reduced, may be explained by the different effector mechanisms of these substances. Prostaglandin E1 acts via specific receptors on the cell surface, whereas calcitonin gene-related peptide relaxes smooth muscles by hyperpolarization, most likely induced by potassium channel opening.²⁸ Furthermore, calcitonin gene-related peptide seems to stimulate the production of cyclic adenosine monophosphate, resulting in smooth muscle relaxation.²⁹

In addition to the potentiating effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 regarding erectile response, a pain reducing effect of the combination compared to prostaglandin E1 alone has been described previously. This low rate of pain during and/or after the intracavernous injection was reproduced in our series with only 2 of 65 patients (3%) experiencing pain after the injection of the combination of calcitonin gene-related peptide plus prostaglandin E1. This 3% rate is significantly lower than the 20 to 30% rate after prostaglandin E1 alone.¹³ The pain reducing effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 may be due to the reduction of the amount of prostaglandin E1 in the combination compared to the application of prostaglandin E1 alone, as well as the anti-inflammatory effect of calcitonin gene-related peptide itself.³⁰

The results of this clinical experimental study on patients with erectile dysfunction who are either not responding to papaverine-phenolamine or in whom cavernous fibrosis develops due to papaverine-phenolamine suggest a possible beneficial effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 for intracavernous injection. Because of the experimental nature of our study patients should be carefully selected and followed closely.

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